

Glycogen Storage Diseases and Cardiomyopathy

TO THE EDITOR: Arad et al. (Jan. 27 issue)¹ report that *LAMP2* mutations (Danon's disease) are an important cause of hypertrophic cardiomyopathy. That one of their patients had an "adolescent response to cardiac disease," however, strangely misses the point that mental retardation commonly accompanies this disease. Both of the patients in the original cases described by Danon et al.² had mental retardation, and in a series of 38 patients, described by Sugie et al.,³ 70 percent of male patients (14 of 20) and 6 percent of female patients (1 of 18) had mental retardation. Lohrbrin et al.⁴ and Sugie et al.⁵ have also reported that patients with Danon's disease did not reach other neurodevelopmental milestones — most with this disease did not walk until they were 18 months old and many had learning difficulties.

We recommend that patients who present with hypertrophic cardiomyopathy be asked about their educational performance. If there is a history of learning difficulties, they should be referred for further evaluation. If a diagnosis of Danon's disease is made, all first-degree relatives should be offered genetic testing and stratification of the risk of sudden death from cardiac causes.

Jonathan C.P. Roos, M.A.
Timothy M. Cox, M.D.

University of Cambridge
Cambridge CB2 2QQ, United Kingdom

1. Arad M, Maron BJ, Gorham JM, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med* 2005;352:362-72.
2. Danon MJ, Oh SJ, DiMauro S, et al. Lysosomal glycogen storage disease with normal acid maltase. *Neurology* 1981;31:51-7.
3. Sugie K, Yamamoto A, Murayama K, et al. Clinicopathological features of genetically confirmed Danon disease. *Neurology* 2002;58:1773-8.
4. Lohrbrin JA, Schorderet DF, Payot M, et al. Morphological, clinical and genetic aspects in a family with a novel *LAMP2* gene mutation (Danon disease). *Neuromuscul Disord* 2005;15:293-8.
5. Sugie K, Koori T, Yamamoto A, et al. Characterization of Danon disease in a male patient and his affected mother. *Neuromuscul Disord* 2003;13:708-11.

THE AUTHORS REPLY: Roos and Cox "recommend that patients who present with hypertrophic cardiomyopathy be asked about their educational performance." We concur. However, our article goes further, suggesting that other clinical findings, such as preexcitation on the electrocardiogram or elevated levels of creatine kinase, should also trigger evaluation of *LAMP2* and *PRKAG2* genes. The central theme of our article is that whereas many *LAMP2* mutations cause Danon's disease, with its associated neurologic and muscular abnormalities, some *LAMP2* mutations produce primary cardiac disease that mimics hypertrophic cardiomyopathy without neuromuscular or behavioral abnormalities. Only two of the six patients in our study had even mild behavioral or psychological abnormalities — relatively common problems among adolescents with cardiac disease.¹ If these patients had been cared for according to standard cardiologic practice,² which does not include genetic testing,³ the cause of their cardiomyopathy would not have been identified.

Michael Arad, M.D.

Sheba Medical Center
Tel Hashomer 52662, Israel

Barry J. Maron, M.D.

Minneapolis Heart Institute Foundation
Minneapolis, MN 55407

J.G. Seidman, Ph.D.

Harvard Medical School
Boston, MA 02115
seidman@genetics.med.harvard.edu

1. Wray J, Long T, Radley-Smith R, Yacoub M. Returning to school after heart or heart-lung transplantation: how well do children adjust? *Transplantation* 2001;72:100-6.
2. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003;42:1687-713.
3. Maron BJ, Seidman JG, Seidman CE. Proposal for contemporary screening strategies in families with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2004;44:2125-32.

What Ails the FDA?

TO THE EDITOR: Okie's Perspective article (March 17 issue)¹ on the Food and Drug Administration (FDA) covers important ground but misses a key issue. No drug is absolutely safe; drug safety is always as-

essed in relation to the disease being treated. We tolerate greater risk from beneficial therapy when the alternatives are bad.

Risk-benefit analysis requires us to define the

target population for the drug. Clinical trials are the best way to define this population. Direct-to-consumer marketing campaigns, on which drug companies spend billions of dollars, circumvent this process and often encourage patients to demand prescription drugs inappropriately. Rofecoxib (Vioxx) was an important beneficiary of such a campaign. As a result, many people were put at risk although their medical needs could have been met with less toxic drugs.

Today, patients for whom rofecoxib provided the best relief are no longer able to obtain it. In short, pharmaceutical-company greed created an unmet medical need. There is a cost-free way to help the FDA protect patients: stop direct-to-consumer advertising and let trained and knowledgeable physicians determine the best treatment for our patients.

Kenneth J. Gorelick, M.D.

1 Maplewood Dr.
Newtown Square, PA 19073

1. Okie S. What ails the FDA? *N Engl J Med* 2005;352:1063-6.

TO THE EDITOR: What ails the FDA is the political influence that limits the agency's resources and interferes with its regulatory decisions.¹⁻³ The FDA has always been underfunded and understaffed in relation to the scope of its responsibilities.¹ Surveillance of drug safety has been impaired by a decrease in the personnel and resources devoted to it because of the emphasis on the rapid review of new drugs and unfunded congressional mandates. The other problems noted by Okie — intimidation of staff scientists, weak leadership, and the pro-industry bias of the former chief counsel — are manifestations of the political manipulation of the FDA by the administration.

Two changes are necessary to restore the FDA to health: a budget that is commensurate with its responsibilities and scientific independence. The FDA could be shielded from political manipulation through the appointment of an independent scientific advisory board to advise Congress about the performance and needs of the agency. By making its recommendations public, the advisory board could help Congress to resist pressure from lobbyists and advocacy groups.

Donald M. Marcus, M.D.

Baylor College of Medicine
Houston, TX 77030
dmarcus@bcm.tmc.edu

1. Hilts PJ. Protecting America's health: the FDA, business, and one hundred years of regulation. *New York: Alfred A. Knopf*, 2003:117-28.
2. Drazen JM, Greene MF, Wood AJJ. The FDA, politics, and Plan B. *N Engl J Med* 2004;350:1561-2.
3. Harris G. Regulation redefined: the F.D.A. shifts focus: at F.D.A., strong drug ties and less monitoring. *New York Times*. December 6, 2004:A1.

TO THE EDITOR: Okie's article could lead the reader to the conclusion that an independent drug-safety agency would protect patients better. But Okie omits certain events surrounding the withdrawal of rofecoxib from the market that illustrate the potential downside of separating the FDA's drug-approval function from post-marketing safety surveillance. In particular, she does not mention the fact that experts in drug safety and the relevant therapeutic field who gathered at an FDA advisory committee meeting in February to discuss the safety of cyclooxygenase-2 (COX-2) inhibitors and nonsteroidal antiinflammatory drugs (NSAIDs) voted 17 to 15 that rofecoxib ought to be allowed to be marketed. Nor did Okie mention that David Graham, the FDA epidemiologist who has heartily criticized the agency's handling of the rofecoxib review, is rather more certain in his views of the benefit-risk equation for the drug; he has said that "there really doesn't appear to be a need for COX-2 selective NSAIDs." The point is that drug-safety experts tend to downplay therapeutic benefits, and clinical practitioners tend to downplay risks. What is needed at the FDA is an unrestrained voice for experts on both sides of the equation.

Fredric J. Cohen, M.D.

Crownstone Investment Research and Consulting
Bensalem, PA 19020
fred@crownstonegroup.com

TO THE EDITOR: To redress the institutionalized influence of the pharmaceutical industry on the FDA's drug-approval process, perhaps third-party payers such as insurance companies and health maintenance organizations need to be invited to join the fray. These payers cover not only the costs of expensive new technology, but also any costs incurred because of unanticipated adverse effects. Who is more motivated to expose problems with efficacy and safety that are deliberately obscured by the pharmaceutical industry? Rather than perpetuate the sham of an unbiased partnership between government and industry committed to protecting and enhancing health, why not expose the powerful fi-

nancial motivations that drive health care decisions? If drug companies are treated as agents of science and discovery, payers ought to be viewed as the corrective agents of scientific scrutiny. A more open discourse involving parties with admittedly different agendas may more successfully illuminate the

issues critical to decisions that have consequences for public health and public coffers.

Elizabeth R. Jenny-Avital, M.D.

Albert Einstein College of Medicine
Bronx, NY 10461
jennyavita@earthlink.net

Obesity and Longevity

TO THE EDITOR: Preston's editorial (March 17 issue)¹ on obesity and its influence on longevity, which accompanies the report by Olshansky et al.,² focused my thinking on morbidity versus mortality. Preston wrote that "the current life expectancy at birth in the United States would be one third to three quarters of a year higher if all overweight adults were to attain their ideal weight." This goal is unlikely to be achieved, and even if it were, the gain in life expectancy would be minuscule. As a clinician, however, I see daily the terrible morbidity that obese patients have — complications from diabetes, dyslipidemia and hypertension, wear and tear on the knees and hips, legs swollen from venous insufficiency, backache, and a winding down of physical activity. It seems to me that an emphasis on morbid states that could be averted with the elimination of some (not all) excess weight would permit an educable patient to sit up, take notice, and act. The gain in life expectancy is too small to sell to any patient. The avoidance of suffering is worth the effort.

Fred W. Whitehouse, M.D.

Henry Ford Hospital
Detroit, MI 48202
fwhiteh1@hfhs.org

1. Preston SH. Deadweight? — the influence of obesity on longevity. *N Engl J Med* 2005;352:1135-7.
2. Olshansky SJ, Passaro DJ, Hershaw RC, et al. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med* 2005;352:1138-45.

TO THE EDITOR: In providing examples of population shifts toward healthier lifestyles, Dr. Preston states incorrectly that "primarily because of behavioral changes, the incidence of AIDS has fallen by nearly 50 percent since 1992." The observed decline in the incidence of AIDS from 1992 to 1994 was an artifact of the change in the surveillance case definition for AIDS that was implemented in January 1993.¹ A substantial decline was then observed in the years 1995 through 1998 after the introduction of highly active antiretroviral therapy for hu-

man immunodeficiency virus (HIV) infection.² Since 1998, the incidence of AIDS has remained relatively stable.² To suggest a shift toward "healthier lifestyles" in the context of HIV infection is particularly misleading, given recent reports of increased levels of unsafe sexual behavior among gay and bisexual men in urban centers throughout the United States, Canada, and Western Europe.³ These reports highlight the critical need for continued efforts to identify and implement more effective strategies of HIV prevention.

Paul A. Simon, M.D., M.P.H.

Douglas M. Frye, M.D., M.P.H.

Los Angeles County Department of Health Services
Los Angeles, CA 90012
psimon@ladhs.org

1. Update: acquired immunodeficiency syndrome — United States, 1994. *MMWR Morb Mortal Wkly Rep* 1995;44:64-7.
2. Advancing HIV prevention: new strategies for a changing epidemic — United States, 2003. *MMWR Morb Mortal Wkly Rep* 2003; 52:329-32.
3. Golden MR, Marra CM, Holmes KK. Update on syphilis: resurgence of an old problem. *JAMA* 2003;290:1510-4.

TO THE EDITOR: Preston states, regarding obesity, that "the U.S. population has already shown the ability to shift to healthier lifestyles." There are few recent data to support his statement. During the past 15 years, the percentage of adults who smoke has decreased by only 1 percent.¹ The number of new cases of AIDS has remained unchanged, at 40,000 per year.² The modest reduction in the number of fatal vehicular crashes reflects improved safety equipment and better emergency medical care, not fewer drunk drivers.³ The incidence of obesity has doubled, dietary fat intake has increased, and serum cholesterol levels have not decreased significantly (from 205 to 203 mg per deciliter).⁴

An antiobesity campaign should focus sharply on creating new social policies that encourage weight loss (e.g., adjustments in insurance premiums, compulsory exercise for students from ele-